

Infrared Absorption Spectra of a Series of 2, 6-diamino and 2-amino-6hydroxy-8-choroalkyl Purines

I.M. EJIMADU
Department of Chemistry
University of Benin
Benin City, Nigeria.

Keywords: Infrared analysis, purines, synthesise, melting point, absorption spectra

ABSTRAK

8 purina haloalki disintesis dan diuji dengan menggunakan analisis inframerah (IR). Sintesis dan analisis inframerah tersebut dicatatkan. Kajian ke atas purina tersebut merangkumi (i) 2,6-diamino-8-purina-Klorometil, (ii) 2,6-diamino-8-purina kloretil, (iii) 2,6-diamino-8-purina kloropropil, (iv) 2-amino-6-hidroksil-8-purina korotil, (v) purina 2-amino-6-hidroksil 8 purina (3-kloropropil). Penyerapan I_{max} ultra ungu terhadap purina tersebut diambil pada μ^{H11} dan keputusannya dibentangkan. Tahap kecairan dan elemen analisisnya turut dibentangkan. Spektra inframerah (inframerah dalam KBr) C-8 diganti 2, 6-diamino; 5 or 2-amoni 6-purina hidroksi, 6 dibandingkan dengan 7 inframerah pteridin; 8; benzimidazola, 9; pirrois, 10; indole, 11 (Jadual I, II, III dan rajah 1, 2, 3, 4, 5 dan 6). Rajah 4 dibentangkan untuk dikaitkan purina baru tersebut dengan (i) hati semula jadi L. faktor casei, (A) (ii) hati sintetik L. faktor casei (asid Rasemik pteroylgutamik (C) (v) hati sintetik rasemik L. faktor casei, asid pterylgutamik rasemik (D) (iv) Hati rasemik semula jadi L. casei faktor asid pteroik (E).

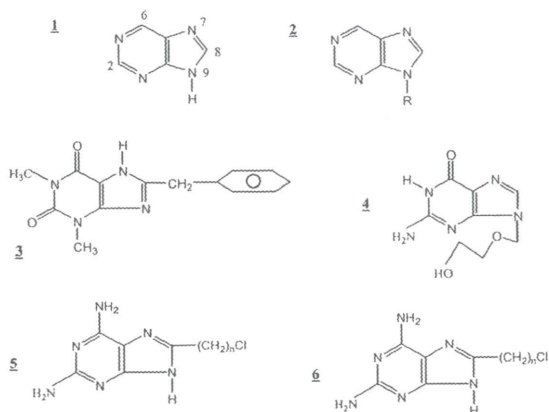
ABSTRACT

8-haloalkyl purines were synthesized and infrared analysis (IR) carried out on them. The syntheses as well as the IR analyses are reported. The purines synthesized and studied include (i) 2,6-diamino-8-Chloromethyl purines, (ii) 2,6-diamino-8-chlorethyl purine, (iii) 2,6-diamino-8-chloropropyl purine, (iv) 2-amino-6-hydroxyl-8-chloroethyl purine, (v) 2-amino-6-hydroxyl 8-(3-chloropropyl) purine. The ultra violet UV I_{max} absorption of these purines were taken at μ^{H11} and results are presented. The melting points and their elemental analyses are also presented. The IR (infrared in KBr) spectra of C-8 substituted 2, 6-diamino; 5 or 2-amino -6hydroxy purines, 6 are compared to the IR spectra of pteridines 7; 8; benzimidazole, 9; Pyrroles, 10; indole, 11 (Tables I, II, III and figures 1, 2, 3, 5 and 6). Figure 4 is presented to relate these novel purines to (i) natural liver L. casei factor (A) (ii) synthetic liver L. casei factor (Racemic pteroylgutamic acid (C) (v) Synthetic racemic liver L. casei factor, racemic pteroylgutamic acid (D) (iv) Natural racemic liver L. casei factor pterioic acid (E).

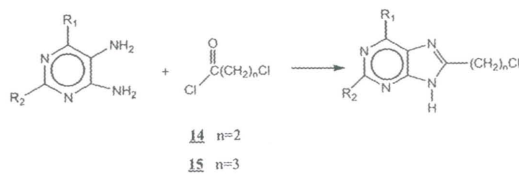
INTRODUCTION

Purines 1 and derivatives 2, 3, and 4 are in use in medicine as drugs (Daly 1985). Adenosine 2 (a purine nucleoside) is known to demonstrate cardiovascular, nervous and endocrine activities. 8-benzyl theopylluine 3 has vassopresor activity (Chemical and Eng. News 1986); Brigden *et al.* (1981), Maylor *et al.* (1961). Acycloguanosine, 4 (a purine nucleoside (Martins *et al.* 1985). 2, 6-diamino-8-chloroalkyl purines, 5 and 2-amino-6-hydroxy-8-chloroalkyl purines, 6 are a new series of purines related to the adenosines 2 and unlike

adenosines have received limited investigations as therapeutic agents (Ejimadu 1988). It is expected that these new purines will physiologically mimic adenosines or analogs on account of their structural (or 2-amino -6) hydroxy groups of drugs. C₈ - haloalkyl substituted 2, 6 -diamino (or 2-amino - 6 hydroxy) purines are good alkylating agents for N-nuceophiles (functional group modifying agents, (Ejimadu 1992) and may become good antineoplastiv agents, just like many anticancer alkylators e.g. mitomycins. Their N₉ - if



SYNTHESIS



- 5a:** R1 = R2 = NH2 (n=1) **5b:** R1 = R2 = NH2 (n=2)
5c: R1 = R2 = NH2 (n=3)
6a: R1 = OH; R2 = NH2 (n=2) **6b:** R1 = OH; R2 = NH2 (n=2)
12: R1 = R2 = NH2 **13:** R1 = OH; R2 = NH2
14: n = 2 **15:** n = 3

glycosylated with N₉ sugar analogs **4** may confer anti viral activity on these new purines (Martins 1985; Watt 1990; Schaeffer *et al.* 1978).

It is therefore significant to present the Infrared spectra of these new purines **5**. and **6** which are lacking in the literature.

MATERIALS AND METHODS

The melting points were taken on a melting point apparatus and were uncorrected. The ultra violet lmax values were obtained on Beckman DB-9 and infrared (IR) analyses of products were taken on a Nicolet model 700 FTIR interferometer and absorption frequencies reported in cm⁻¹. Elemental analysis (C, H, N) was done by Atlantic Micro Laboratories Inc. Atlanta Georgia, USA.

The following reagents used for reactions were purchased from Aldrich Chemical Company.

- 2, 6-triamino-4-hydroxy pyrimidine sulphate salt.
- 2, 4, 5, 6-tetraamino pyrimidine sulphate salt.

- 4-chlorobutyl chloride
- 3-chloropropionyl chloride

2, 6-diamino-8-chloromethyl purine **5**, (a=1)

2, 4, 5, 6-tetra-amino pyrimidine sulphate salt 92.1g,; 0.01 mole) solid was thoroughly mixed in a mortar with chloroacetic acid (4.7 g; 0.05 mole). The mix was taken in a 250 mL round bottom flask. A water aspirator was then attached to this flask (an arrangement to evacuate water produced by the reaction), so as to subject the reaction to some vacuum. The flask with its contents was heated for 2 hrs and allowed to cool. The reaction mixture was washed with diethyl ether (930 mL) for three consecutive times to remove excess (unreacted) chloroacetic acid. The residue was taken in 50 mL of water and filtered (while hot). Fine crystals were obtained on cooling the filtrate. The crystals weighed 0.72 g (32.2% yield). UV λ_{max} 290 nm at P^H11.

IR (Kbr) cm⁻¹ 3415, 3269, 3154, (-NH₂, -NH) 3020, 2971, 2809 (-CH₂-Cl)

Elemental analysis

Calculated C, 30.71 H, 4.72 N, 35.81
Cl, 15.11

Found C, 30.99 H, 4.92 N, 36.68
Cl, 15.42

Molecular formula: C₆H₇N₆Cl.2H₂O

2, 6-dimino-8-chloroethyl purines **5**, (n=2)

2, 4, 5, 6-tetraamino Pyrimidine sulphate- (7 g; 0.08 mole) was dissolved in 2 M NaOH (100 mL) in a 250 mL round bottom flask and an undertermined quantity of ice chips added to the solution. The outside of the reaction flask was also surrounded with ice blocks.

3-chloropropionyl chloride (7 mL; 0.08 mole; 2-equivalents) was added to the flask through an injection needle in two disproportionate batches (4 mL followed by 3 mL later) and vigorously stirred (magnetic stirrer). The flask was stoppered and stirring continued until it became difficult to continue the stirring (because the reaction mixture was very syrupy). The reaction lasted for 20 min and was worked up by filtering with abuchner funnel attached to a powerful water aspirator (to provide sufficient suction pressure). The residue was dissolved in ammonium hydroxide and filtered (hot). A dry weight of crystal of 2.06 g, 20.0% yield. (oven dried at 100°C) was obtained. UV lmax 300nm at P^H.11.

IR KBr cm⁻¹ 3400, 3344, 3203, 3014 (-NH₂;
- NH) 2956, 2886, 2745 (-CH₂- Cl)

Elemental analysis:

Calculated C, 33.81 H, 5.23 N,
33.70 Cl, 14.28

Found C, 33.59 H, 5.31 N,
33.61 Cl, 14.20

Molecular formula C₇H₉N₆Cl.2H₂O

$$\frac{C}{N} \text{ ratio } (b) = 1.20$$

Molecular formula: C₈H₁₀ON₅Cl.2 1/2 H₂O

RESULTS AND DISCUSSION

The infrared absorption spectra of these new agents (*Figs. 2, 3, 5 and 6*) present definite regional difference with those of related benzimidazoles **9** but maintain some semblance with pteridine derivatives (Mowat *et al.* 1947; Waller 1948; Taylor and Dumas 1982) e.g. 2 - amino - 4 - hydroxy - 6 - methyl pteridines, **7**, and folic acid, **8** (*Figs. 7 and 4*). Hitchings *et al.* (1949).

2,6-diamino-8-chloropropyl purine, **5**, (n=3)

This compound was made in the same way as for 2, 6-diamino-8-chloro ethyl purines **5**, 9n=2) using 2, 4, 5, 6-tetraamino pyrimidine sulphate salt. 96g; 0.023 mol) and 4-chlorobutyl chloride (0.05 mole; 2 equivalents). A dry weight of 1.66g (31.3% yield) of expected product was obtained after crystallation (hot water).

UV lmax 292nm at pH11.

IR KBr cm⁻¹ 3492, 3386, 3344, 3154 (-NH₂;-NH), 2985, 2942, 2816 (-CH₂Cl), Elemental analysis:

Calculated C, 39.26 H, 5.32 N, 34.35 Cl,
14.15 (a)

Found C, 39.15 H, 5.36 n, 34.98 Cl.,
1291 (b)

$$\frac{C}{N} \text{ ratio } (a) = 1.14$$

$$\frac{C}{N} \text{ ratio } (b) = 1.12$$

Molecular formula: C₈H₁₁N₆Cl.H₂O

2-amino-6-hydroxyl-8-chloro ethyl purine **6**, (n=2)

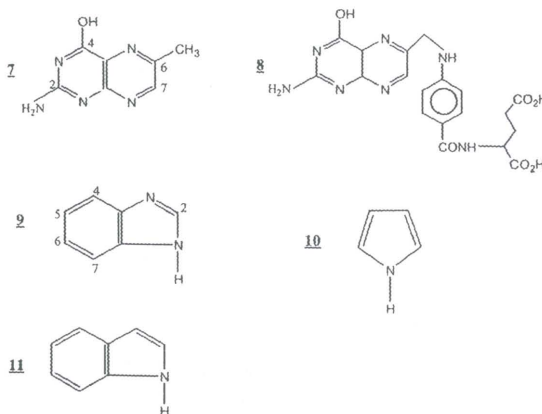
2, 5, 6-triamino-4-hydroxy pyrimidine sulphate salt **13** (6g, 0.025 mole) was dissolved in 2M H₂SO₄ (50 mL) in 100 mL round bottom flask (with some chips of ice inside and outside the flask as in the case for 2, 6-diamino-8-chloroethyl purine **5** (n=2)). 2-chloro propionyl chloride **14** (6.24 ml, 0.05 mole, 2-equivalents) was introduced into the flask and stirred. A similar work up procedure was followed as for **5b** (n=2). The product obtained weighed 4.07 g (65.02% yield) after hot water recrystallisation **10**

UVlmax 292nm at pH11.

IR KBr cm⁻¹ 3400, 3337, (-NH₂;-NH) 2858, 2745 (-CH₂-) 744 (-CH₂-Cl) Elemental analysis:
Calculated C, 33.67 H, 4.84 N, 28.05 Cl, 14.23
9a0

Found C, 33.34 H, 4.79 N, 27.66 Cl, 13.66 (b)

$$\frac{C}{N} \text{ ratio } (a) = 1.20$$



Hydrogen bonding between N₇ and N₉ positions of neighbouring purines has been put forward to rationalize the high melting point of purines (213°C) lin, T *et al.* (1984). The purines were therefore thought to exist as chains of molecules (in the solid phase) because of the extensive hydrogen bonding. Hydrogen bonding of the kind N-H ...N has been used to explain the absence of absorption in the normal stretching region (i.e. 3400 cm⁻¹) in benzimidazoles, **9** (close relatives of the purines) in solid specimens (Morgan 1961) (*Fig. 8*). Hydrogen bonding apparently is not operative for these purines in KBr (Potassium bromide).

DISCUSSION

The infrared spectra and bands of these novel compounds (Tables 1, 2, 3 and *Figs. 1, 2, 3, 5 and 6*) present clear pictures of the N-H stretching region and other regions of the

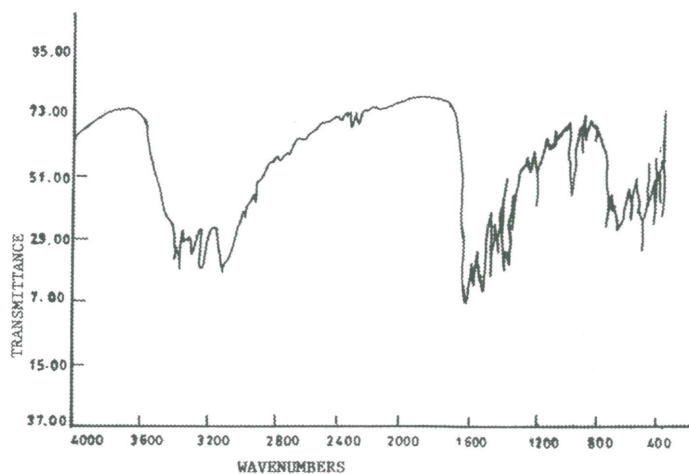


Fig. 1: IR-absorption spectra of 2,6 – diamino-8-chloromethyl purine

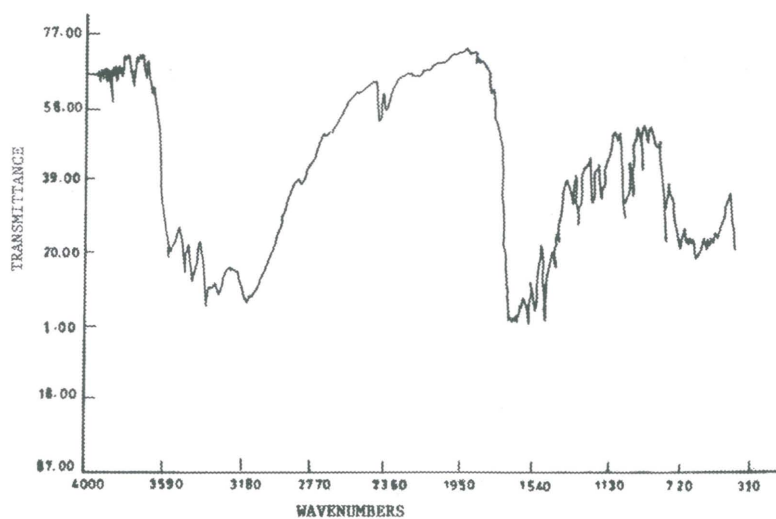


Fig. 2: IR-absorption spectra of 2,6 – diamino-8-chloroethyl purine

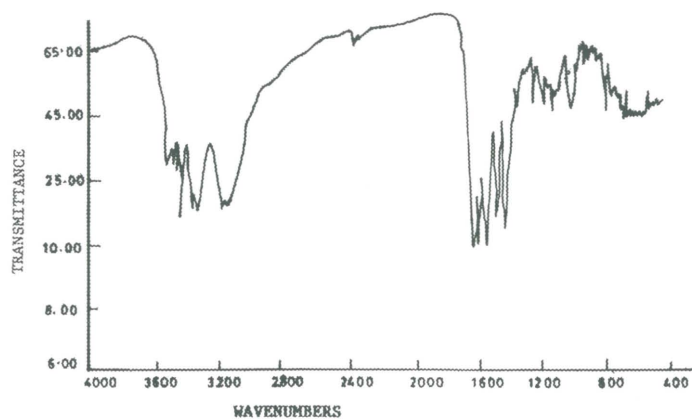


Fig. 3: IR-absorption spectra of 2,6 – diamino-8-chloropropyl purine

INFRARED ABSORPTION SPECTRA OF A SERIES OF PURINES

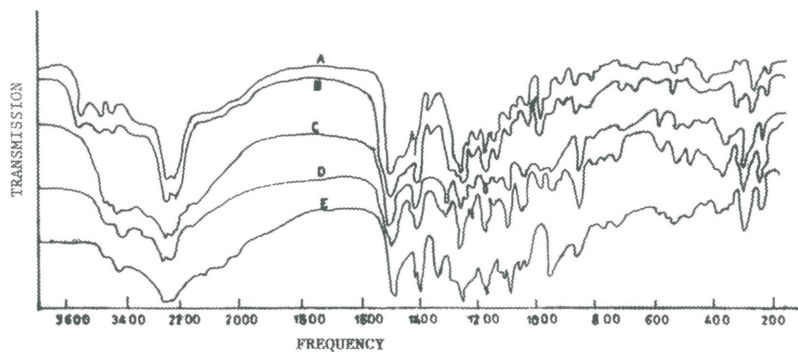


Fig. 4: Infrared absorption Spectra A natural Liver L. Casei factor B. Synthetic Liver L. Casei factor or (pteroylglutamic acid) C. Synthetic racemic Liver L. Casei factor (racemic pteroylglutamic acid); D. natural racemic Liver L. Casei factor E. pterioic acid. (II)

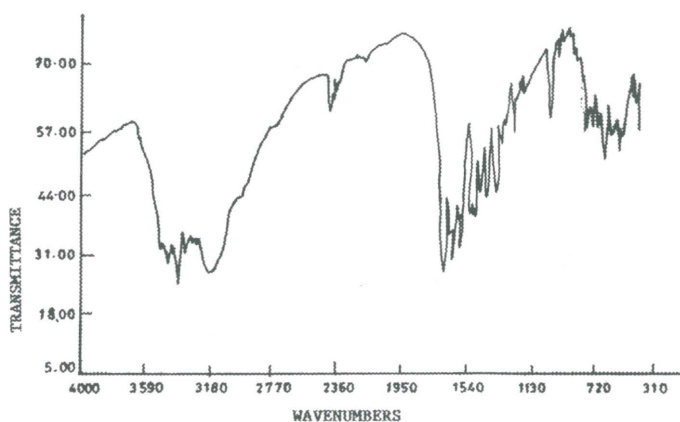


Fig. 5: IR-absorption spectra of 2-amino-6-hydroxy-8-chloroethyl purine (Guanine)

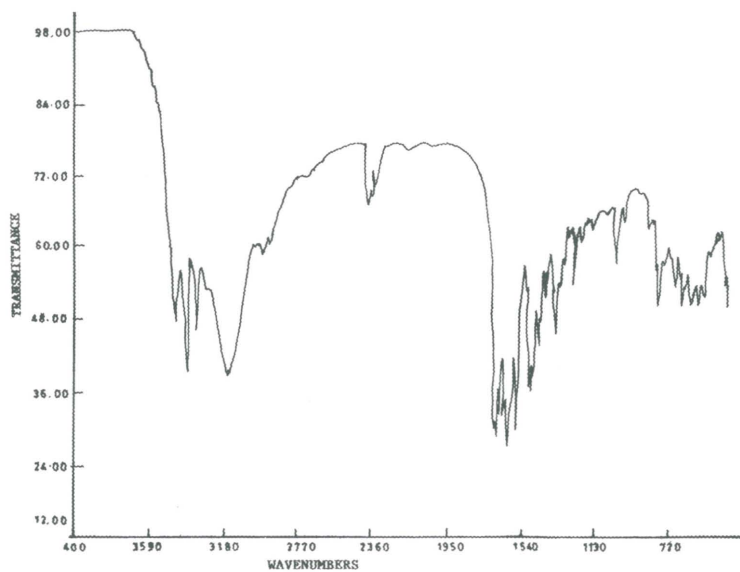


Fig. 6: IR-absorption spectra of 2-amino-6-hydroxy-8-chlorophenyl purine (Guanine)

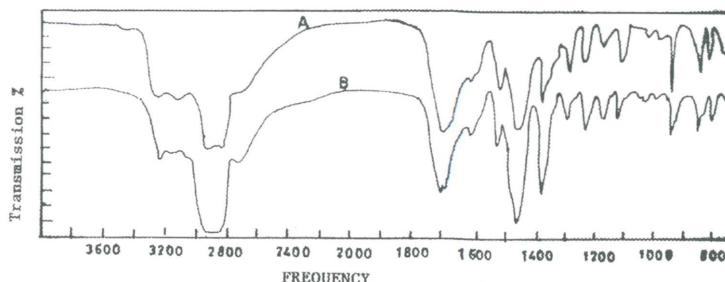


Fig. 7: IR-absorption spectra of 2-amino-4-hydroxy-6-methyl pteridine (10)
A: Natural B: Synthetic

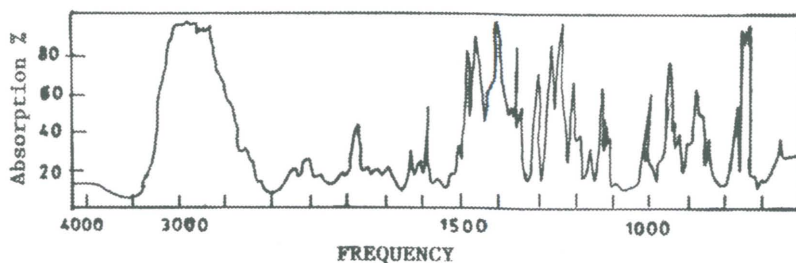


Fig. 8: IR-absorption spectra of Benzimidazole (7)

TABLE 1

IR absorption bands and melting point of 2, 6-diamino-8-chloroalkyl purines (3000-4000cm⁻¹)

n	IR cm-1 (KBr)	m.p
1	3415, 3337, 3269, 3154, 3020 – NH ₂ ,NH	300°C
2	3400, 3344, 3202, 3147 – NH ₂ ,NH	300°C

TABLE 2

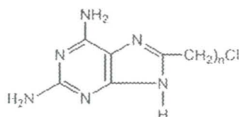
IR absorption bands and melting point of 2-amino-6-hydroxy-8-chloroalkyl purines (3000-4000cm⁻¹)

n	IR cm -1 (KBr)	m.p
1	---	---
2	3464, 3450, 3339, 3281, 3125, - OH, -NH ₂ , - NH	300 C
3	3450, 3393, 3380, 3374, 3168, 3006 -OH, -NH ₂ , -NH	300 C

TABLE 3

Other bands (3000 – 600 cm⁻¹) diagram

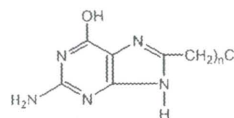
A



cont. TABLE 3

n	IR cm-1 KBr
1	2971, 2809, 1647, 1618, 1590, 1569, 1520, 1492, 1449, 1435, 1400, 1315, 1259, 1238, 175, 1020, 981, 963, 780, 710, 639
2	2956, 2886, 2745, 2661, 1660, 1618, 1561, 1498, 1449, 1399, 1378, 1308, 1272, 1202, 1160, 1019, 984, 934, 892, 786, 709, 666
3	2985, 2942, 2921, 2816, 1646, 1611, 1561, 1498, 1449, 1371, 1285, 1209, 1174, 1146, 1089, 1005, 984, 927, 899, 843, 786, 666

B



n	IR cm-1 KBr
1	2971, 2928, (-CH ₂ -), 1681, 1632, 1575, 1484, 1449, 1406, 1315, 1237, 1216, 1153, 1012, 927, 892, 772, 702, (-CH ₂ Cl), 652
2	2971, 2935, (CH ₂ -), 1681, 1632, 1575, 1484, 1449, 1408, 1348, 1300, 1237, 1209, 1106, 1012, 989, 778, 695, (-CH ₂ Cl), 652

different molecules. The normal N-H bands at 3400 cm^{-1} are unaffected by the medium in which these purines were dispersed for their infrared spectral determinations (i.e. KBr). This band (3400 cm^{-1}) is seen only in solutions of benzimidazole spectra. The spectra 90.1 mole/L 9, pyrroles 10 and indoles, 11 as simple in the region $2400\text{--}3200\text{ cm}^{-1}$ for solid specimens (e.g. Fig. 8) (Morgan 1961). The use of KBr (for benzimidazoles) is known to cause no significant change in benzimidazole spectra. The spectra of these purines 5 9a, b, c) are being reported for the first time. It is interesting to note that the region of the spectra $3000\text{--}4000\text{ cm}^{-1}$ are similar in both the purines (e.g. 2 - amino-6 - hydroxy derivatives, Figs. 5, 6) and in the pteridine seriesw 9pteroyl glutamic acid - Fig. 4, and 2-amino - 4 - hydroxy-6 -methyl pteridine- Fig. 7; Waller *et al.* (1948); Wein Stock *et al.* (1970).

The replacement of 6- Oh group (in the pteridines) with -NH_2 group does not create a marked difference in the shape of the spectra (even though -OH and -NH_2 groups absorb at different frequencies).

The contrast in the shape of the spectra in this region ($3200\text{ to }4000\text{ cm}^{-1}$) for the diamino or amino - hydroxy purines and the benzimidazole is a consequence of replacement of pyrimidine component (fused to imidazole in benzimidazole - Figs. 1, 2, 3, 5, 6 compared with Fig. 8).

The melting point for purines 5 and 6 are high and range from $259\text{--}300^\circ\text{C}$. The purines melt lower (140°C).

ACKNOWLEDGEMENTS

The author thanks Professor T.J. Bardors, Drs. T.I. Kalman and L. Fedor (all of the State University of New York at Buffalo) for their directive roles in execution of the project. The State University at Buffalo is acknowledged for the use of the equipments.

REFERENCES

- BRIGDEN, D., P. FIDDIAN and A. ROSLING. 1981. Acyclo vir-a review of the preclical and early data of a new antiherpes drug. *Antiviral I*: 203-212.
- DALY, J. N., W. PADGET, M. T. SHAMIN, P. BUTTS - LAMB and J. WATERS. 1985. 1, 3 - dialkly - 8 - (P-Sulfophenyl). Xanthines. Potent Water soluble antagonists for A_1 - and A_2 - adenosine receptor. *J. Med Chem.* **28**: 482-487.
- EJIMADU, I. M. 1988. Molecular modification in modern drug research (Design and synthesis of purine anti - neoplastic agents. *Nigerian J. Appl. Science (NJAS)* **6(2)**: 09 - 124.
- EJIMADU, I. M. 1992. Purine alkylating agents - 2, 6 - diamino - 8- haloakyl purines (Potential antimalarials). *J. Sci. I. R. Iran.* **3**: 101-106.
- HITCHINGS, G. H. and G. B. ELION. 1949. Komeriic dihydroxanth opterins *J. Am. Chem Soc.* **71**: 467.
- MARTINS, J. C. 1985. Synthesis of 9 - (4-hydroxy-2-oxobutyl guanines, 9-(2,4-dihydroxybutyl) guanine and related acyclic nucleoside analogues. *J. Org. Chem.* **50**: 755-759.
- MAYLOR, R. N., G. SHOW and D. N. BUTTER. 1961. Purines, pyrimidines and imdazoles and derivatives 9- amino purines *J. Chem. Soc.* 4845.
- MORGAN, K. J. 1961. The infrared spectra of some simple Benzimidazones. *Journal of the Chemical Society Part 11*: 2343-2347.
- SCHAEFFER, H. J., L. BEAUCHAMP, P. DE MIRANDA, G. B. ELION, D. J. BAUER and P. COLLINS. 1978. 9-(2-hydroxy ethoxy methyl) guanine activity viruses of the Herpes group. *Nature* **272**: 583-585.
- Chemical and Engineering News. 1986. Some guanines and adenosine analogs inhibit both RNA and DNA viruses (special report). **27**: 34.
- TAYLOR, E. C. and D. J. DUMAS. 1982. Pteridines 49. Synthesis of 2,4 diamino - 6, 8-dihrdoxy - 7- aryl-8- oxopytrollo (3,4-g) pteridines. *J. Org. Chem.* **47**: 116-119.
- WALLER, C. W., B. L. HITCHINGS, J. H. MOWAT, E. L. R STOKSTAD, J. H. BOOTHE, R. B. ANGIER, J. SEMB, Y. SUBBAROW, D. B. COSULICH, M. J. FAHRENBACH, M. E. HULTQUIST, E. KUH, E. H.

- NORTHEY, D. R. SEEGER, J. P. SICKILS and J. M. SMITH JR. 1948. Synthesis of pteroylglutamic acid (liver I. casie factor) and pterioic acid. *J. Am. Chem. Soc.* **70**: 19-22.
- WEIN STOCK, L. T., F. BERNARD and C. C. CHENG. 1970. Folic acid Analogs II. P-{2,6 – diamino – 8- purinyl) methyl} amino benzoyl – L-glumatic acid and related compounds. *IJ. Med. Chem.* **13**: 995-996.
- WYATT. 1990. Synthesis of 9- hydroxy purines – intermediates to novel antiviral acyclo nucleosides. *J. Med. Chem.* **33**: 187.

(Received: 31 May 2002)
(Accepted: 16 October 2003)